UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN - 9 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Final Rule for 4-(Dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine

FROM: Anne E. Lindsay, Director
Registration Division (H7505C)

TO: Douglas D. Campt, Director
Office of Pesticide Programs (H7501C)

Attached is a final rule that a tolerance be established for residues of 4-(dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine (CGA-154281) when used as an inert ingredient (safener) in pesticide formulations containing metolachlor in or on the raw agricultural commodities for which tolerances have been established for metolachlor. The proposed regulation was requested by the Ciba-Geigy Corporation.

This chemical went through the procedures for processing inert ingredient tolerance exemption requests described in the inert ingredient policy statement. Following the initial review of the submission, it was determined that a finite tolerance, rather than an exemption from the requirement of a tolerance, would be required in this instance. The Health Effects Division (HED) and the Environmental Fate and Ecological Effects Division (EFED) have recommended establishing a tolerance for this inert ingredient.

A further determination has been made that the tolerance shall be time-limited, predicated on the submission of two chronic feeding/oncogenicity studies typically used to support the establishment of a tolerance. The rationale for this decision is described below.

The toxicological, ecological and environmental fate data considered in support of the tolerance include:

1. A 90-day rat oral toxicity study with a no-observed-effect level (NOEL) of 100 ppm or 5.0 milligrams (mg)/kilogram (kg)/day. The lowest effect level (LEL) was 300 ppm, with a finding of increased histopathologic incidences of nephrosis in the kidneys of male rats.

2. A 90-day dog oral toxicity study with a NOEL of 5.0 mg/kg/day. An increased mean liver/gallbladder to terminal body weight ratio was noted at the LEL of 50 mg/kg/day.

3. A 21-day rabbit dermal toxicity study with no irritation noted at 5.0 mg/kg/day.

4. A rat developmental effects study with a NOEL for maternal and developmental toxicity of 100 mg/kg/day.

5. Mutagenicity studies including the Micronucleus test (Chinese Hamster), DNA repair studies (rat hepatocytes and human fibroblasts), and Salmonella/mammalian activation gene mutation (Ames) assay were negative with and without metabolic activation.

6. An acute mallard duck oral toxicity study with an LD50 of 2150 mg/kg or greater.

7. An acute bobwhite quail oral toxicity study with an LD50 of 2000 mg/kg or greater.

8. A 96-hour rainbow trout static acute toxicity study with an LC50 of 3.54 mg/liter (L).

9. A 48-hour daphnia magna flow-through acute toxicity study with an EC50 of 11.47 mg/L.

10. Environmental fate studies including hydrolysis, photolysis, aerobic soil metabolism, leaching and soil adsorption/desorption.

The reference dose (RfD), based on the 90-day rat oral toxicity study NOEL of 100 ppm (5.0 mg/kg/day) and the 90-day dog oral toxicity study NOEL of 5.0 mg/kg/day, using a 1000-fold uncertainty factor, is calculated to be 0.0050 mg/kg of body weight (bw)/day.

The theoretical maximum residue contribution (TMRC) from the proposed tolerance for a 1.5-kg daily diet is estimated to be 0.000187 mg/kg-bw/day for the overall U.S. population which represents 3.7 percent of the RfD. None of the TMRC exposure estimates for the most highly exposed population subgroups exceeds 16.2 percent of the RfD.

The Agency does not expect exposure to 4-(dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine under this tolerance to endanger the public health due to:

(1) The lack of demonstrated mutagenicity. 4-(Dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine was established to be non-mutagenic in four separate tests of genetic toxicity.

(2) The large uncertainty factor used in the dietary exposure estimates and establishment of the RfD. The 1000-fold uncertainty factor is used in the risk assessment process whenever chronic data are not available; it incorporates a factor of ten that is routinely used when extrapolations of NOELs from subchronic to chronic studies are made. Incorporation of this large uncertainty factor notwithstanding, the TMRC represents only 3.7 percent of the RfD.

(3) Actual residues being significantly less than the 0.01 ppm tolerance value. The 0.01 ppm tolerance for residues of 4-(dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine was established by utilizing the level of sensitivity of the residue analytical method rather than a measurement of the true concentrations of residues, which could reasonably be expected to be at least ten times less than the tolerance value.

This tolerance is being established as an time-limited tolerance because the Agency does not have data from two chronic feeding/oncogenicity studies which are part of the toxicology data typically required to be submitted in support of a tolerance request. In addition, a structure-activity relationship analysis of 4-(dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine indicated that the chemical may be a potential carcinogen. The above studies will be required to be submitted to the Agency by April 1, 1996. When the Agency receives these chronic feeding/oncogenicity studies it will reassess this tolerance. However, based upon data considered in support of the tolerance and the restriction on exposure offered by a time limitation on the tolerance, the Agency does not believe that this tolerance poses significant risks.

Additionally, a theoretical cancer risk assessment was conducted using a reasonable worst-case carcinogenic potency factor and the TMRC exposure estimate. This risk assessment indicated that a theoretical upper bound estimate of lifetime dietary risk would be in the negligible range. However, this theoretical cancer risk assessment has not been subject to a formal peer-review process, and does not, at this time, constitute suitable grounds for waiving the oncogenicity data requirements.

This tolerance will expire December 1, 1996. Residues not in excess of these tolerances will not be considered actionable if a pesticide containing this inert ingredient is legally applied during the term of a conditional registration and in accordance with the acceptable labeling under a conditional registration.

This tolerance will be revoked if any data indicate such revocation is necessary to protect the public health.

Since no comments were received on the proposed rule, concurrence was not sought on this final rule.

Attached is a copy of the proposed rule and the concurrences on it from the Office of General Counsel, the Environmental Fate and Effects Division, and the Health Effects Division.

Attachments